

REMARKS

Claims 46, 54-77, and 80-107 are pending in the present application. Claims 46, 74 and 76 are amended. Claims 46 and 76 have been amended to indicate that the surfactant, like the medicament, is also in particle form. Claim 76 has been amended to recite an inhaled medicament. Claim 74 has been broadened so that it specifies "providing a mixture of the medicament and the surfactant," rather than requiring that it be "mixed" in the vessel. Support for the present amendments can be found in the application as filed, including at page 5, lines 5-26, and in the Examples.

The present application claims pharmaceutical aerosol formulations comprising non-aqueous, organic HFA propellants, surfactants, and a medicament for inhalation. The medicament and the surfactant are both in particle form, i.e., are formulated as solid particles suspended in an organic propellant, rather than dissolved in an aqueous solution.

In a telephone conference with the undersigned and Dr. Janis K. Fraser on November 13, 2003, the Examiner reiterated the rejection of the pending claims as obvious over WO/91/11495 in view of Neale et al., Sequeira et al., and Meezan et al. Applicants respectfully traverse.

As described in detail in the Applicants' submissions filed August 15, 2003, and September 12, 2003, WO 91/11495, Neale et al., or Sequeira et al., disclose nothing more than the use of non-aqueous organic hydrofluorocarbon propellants with certain surfactants (but not alkyl saccharides). On the other hand, Meezan et al. discloses aqueous formulations: i.e., medicaments and alkyl saccharide surfactants dissolved in an aqueous medium (the formulations utilized in Meezan's examples are formulated in saline).

WO 91/11495 discloses the use of partially fluorinated lower alkanes as propellants, which can be used in combination with surface-active substances including esters of polyalcohols, fatty acids, phospholipids, etc.

Sequeira et al. disclose the use of metered dose inhalers that deliver aerosolized particles suspended in chlorofluorocarbon or non-chlorofluorocarbon propellants "with or without surfactants" (Col. 5, ll. 17-28) (no specific surfactants were disclosed); and the use of aqueous

suspensions that may contain, *inter alia*, “surfactants, e.g., Polysorbate 80” (Col. 5, l. 63 – Col. 6, l. 5).

Neale et al. discloses pharmaceutical compositions comprising an organic, non-aqueous propellant (a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant), a beclomethasone ester monohydrate, and at least 0.015% water by weight. As noted in Neale et al., Col. 1, ll. 55-60:

The presence of water in conventional aerosol formulations is known to be associated with a number of potential problems and it is generally accepted that these preparations be maintained substantially free of water.

The use of water in Neale et al. is disclosed to increase the stability of aerosol formulations containing beclomethasone dipropionate, which form increasingly large particles during storage due to solvate formation. Neale et al. discloses that it is preferable that the formulations be substantially free of surfactants, but surfactants can be used, as a coating on the particles of medicament. Neale et al. lists a number of surfactants at Col. 3, ll. 40-56, all of which are organic compounds including fatty acid derivatives, phospholipids, and the like, that are reasonably soluble in non-polar solvents (e.g., nothing vastly chemically different from those disclosed in WO 91/11495). The miniscule amount of additional water that Neale et al. discloses is used to prevent aggregation of the beclomethasone particles; the water would be associated directly with the medicament molecules, and would be very unlikely to affect the properties of the propellant. The disclosure of Neale et al. is limited to the unique situation posed by the extremely hygroscopic nature of the beclomethasone medicament, and is not reasonably extendable beyond that special case. As noted above, typically, the presence of water in an HFA-based aerosol formulation is undesirable and to be avoided at all cost. Neale et al. is not describing the use of anything that could be termed an “aqueous solution,” but rather merely the inclusion of a vanishingly small amount of water (the final concentrations of water are measured in ppm) to prevent the solvation of the beclomethasone and subsequent aggregation of the beclomethasone particles.

In contrast, Meezan et al. discloses the use of alkyl saccharides as surfactants in aqueous solutions to enhance absorption. Meezan does not disclose, teach, or even remotely suggest the

use of alkyl saccharides as surfactants for use with non-aqueous HFA propellants as claimed in the present application. The typical surfactant has a dual nature: one “end” of the molecule is hydrophobic, while the other “end” is hydrophilic. This dual nature allows the surfactant to surround non-polar particles and suspend them in a polar solvent, and vice-versa. The surfactant molecular hydrophilic or oleophilic strength is typically expressed as the hydrophile lipophile balance (HLB). When the HLB is less than 10, the oleophilic property is stronger. When the HLB is greater than 10, the hydrophilic property is stronger. An HLB of 3 to 6 can form a water/oil colloid. An HLB of 8 to 18 can form an oil/water colloid. An HLB of 13 to 15 increases the washability function and an HLB of 15 to 18 possesses a solubilizing function for a penetrant. Few surfactants work equally well in both directions, their steric structure and the relative strengths of the polar or non-polar ends making them more suited to micelle formation in one orientation (i.e., hydrophobic in, hydrophilic out) than in the other orientation. Meezan et al. teach that alkyl saccharides are effective surfactants, i.e., they increase absorption, of medicaments delivered in an aqueous solution. Meezan suggests the use of surfactants with an HLB of 10 to 20, preferably 11 to 15, which are surfactants having stronger hydrophilic properties. There is nothing in Meezan et al. that would suggest that the alkyl saccharides could be successfully used in a non-aqueous organic media (and certainly a passing reference to the use of the alkyl saccharides to enhance absorption in “aerosols,” in a laundry list of delivery methods that makes no mention of the use of propellants, is insufficient, particularly as “aerosols” can also include non-propellant sprays of aqueous solutions). One of skill in the art, given the guidance of Meezan, would not have been motivated to use a surfactant that enhances absorption of medicaments in aqueous media in order to improve dispersion and flow of a medicament in a non-aqueous, organic HFA based propellant that is adversely affected by the presence of water, such as those claimed in the present application. There is no teaching or suggestion that alkyl saccharides would have similar beneficial function in an organic media.

The Examiner's conclusion of obviousness is based on improper hindsight. As discussed in MPEP § 2143.01, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify

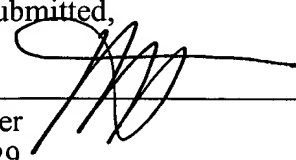
or combine reference teachings. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obvious was improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). The Examiner has provided no objective evidence that one of skill in the art would have been motivated to combine the cited references; the fact that the alkyl saccharides are safe and non-toxic, and function well as absorption-enhancers in aqueous solution, is simply not relevant. There must be some additional motivation, that would actually overcome the knowledge of a skilled artisan, who, familiar with the properties and activities of surfactants and the physical and chemical differences between aqueous solutions (à la Meezan) versus a non-aqueous, organic hydrocarbon propellant (à la Neale, Sequeira, and WO 91/11149), would not have expected that the behavior of an alkyl saccharide dissolved in aqueous solution would be at all similar to its behavior when suspended as dry particles in a non-aqueous, organic media. Thus, there is neither motivation nor expectation of success in the art.

For the foregoing reasons, the Applicants submit that the claims as amended are patentable, and request immediate allowance of the same.

No fee is believed to be due at this time. Please apply any charges or credits to deposit account 06-1050, referencing attorney docket no. 06275-034001.

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Respectfully submitted,



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